

### REMARKS

Claims 28 and 30-46 are pending in the instant application. Claims 28 and 30-46 have been rejected. Claims 30, 31 and 42 have been cancelled. Claims 28, 36 and 40 have been amended to place them in condition for allowance or appeal. Support for these amendments can be found in the specification. After entry of this amendment, Claims 28, 32-41 and 43-46 will remain pending.

#### Rejection of Claims 28 and 30-46 for Obviousness over Dorn et al. (U.S. Patent No. 5,719,147)

The Examiner has rejected Claims 28 and 30-46 under 35 U.S.C. § 103(a) as being obvious over Dorn et al. (U.S. Patent No. 5,719,147). The Applicants respectfully traverse this rejection and provide the following comments.

The Applicants respectfully assert that U.S. Patent No. 5,719,147 (hereinafter "the '147 patent") does not disclose nor suggest the claimed invention, nor would the '147 patent have motivated or enabled one skilled in the art to prepare the subject compounds in accordance with the claimed invention. The Examiner has failed to demonstrate the specific motivation in the '147 patent that would have motivated or directed one of ordinary skill in the art to prepare and utilize the subject compound in accordance with the claimed invention. Applicants respectfully submit that the Examiner has not made a prima facie case of obviousness, such that a showing of secondary indicia of non-obviousness such as unexpected results would be required.

Applicants respectfully request that the Examiner consider the claimed invention as a whole. Applicants respectfully request that the Examiner consider the claimed process in its entirety, including each and every element of the claimed process, as well as how each and every element relates to all of the other elements in the claimed process to prepare the compound 5-[[2(R)-[1(R)-[3,5-bis(trifluoromethyl)-phenyl]ethoxy]-(S)-(4-fluorophenyl)-4-morpholinyl]-methyl]1,2-dihydro-3H-1,2,4-triazol-3-one ["aprepitant"].

Applicants respectfully submit that one of ordinary skill in the art would not have utilized such disclosure in the '147 patent that concerns different reaction processes and synthetic manipulations to provide the claimed invention.

There is no teaching whatsoever in the '147 patent that the conditions employed for such diverse chemical processes to prepare structurally different compounds should be employed in the context of each of the claimed reaction steps to prepare the subject compound 5-[[2(R)-[1(R)-[3,5-bis(trifluoromethyl)-phenyl]ethoxy]-(S)-(4-fluorophenyl)-4-morpholinyl]-methyl]1,2-dihydro-3H-1,2,4-triazol-3-one in accordance with the claimed process. One of ordinary skill in the art would have been presented with a vast number of potential options because the '147 patent would have not given any indication regarding which parameters were critical, nor which direction among the many possible choices would have been successful.

*The instant invention utilizes much less organic solvent and thus results in less organic waste.*

The process of the instant invention utilizes less than half of the organic solvent taught in the '147 patent. For instance, Example 105 (column 136 of the '147 patent) teaches 10 L of dimethylformamide for the reaction of the salt and N-methylcarboxy-2-chloroacetamidrazone, followed by a dilution with 10 L of a mixture of hexanes/methyl-t-butyl ether. After washing and concentrating, the resulting material is dissolved in 20 L of xylenes, and washed with 2 L of hexanes/xylenes. The alternative procedure described in Example 105 (amine TsOH salt starting material) calls for 15.6 L of DMSO, 45 L of MTBE, 25 L of xylenes, 6.35 L of diisopropylethylamine and 13.3 L of methanol. In summary, beginning with 1254g of sulfonate salt requires 42 L of organic solvent, and beginning with 1.90 kg of amine TsOH salt requires 105.25 L of organic solvent.

Conversely, the instant process utilizes 2.2 L of DMSO and 2.5 L of toluene for the reaction of the hydrochloride salt and amidrazone, followed by a dilution with 4 L of toluene. The organic layer is washed with water, and dissolved in 10 L of methanol. In total, starting with 1.00 kg of hydrochloride salt requires 18.7 L of organic solvent.

By reducing the amount of solvent used by more than half, the amount of organic waste products is also reduced. The reduction in solvent used and wasted is more economically efficient than the process described in the '147 patent, and is gentler on the environment.

The "process mass intensity," or "PMI," measures the amount of waste generated for each 1 kilogram of product produced. This metric can be calculated with or without water. For the process described in Example 105 of the '147 patent (beginning with the sulfonate salt), the PMI with water is 142, and 84 without water. For the process described in Example 105 of the '147 patent (beginning with the TsOH salt), the PMI with water is 180, and 76 without water. Conversely, for the process described in the instant invention, the PMI with water is 38, and 17.5 without water.

There is no teaching or motivation in the '147 patent to reduce the amount of solvent used by more than half, nor to choose the particular solvents employed in the instant invention. Even assuming that one skilled in the art did use toluene as a solvent, one would use more than twice the amount to run the reaction.

*The instant invention teaches a process which has less purification steps.*

The process of the instant invention causes the intermediate to remain in solution during the entire reaction, and as a result, has less purification steps. Having less purification steps results in an easier, more efficient process that reduces the opportunities for waste and product loss.

The process taught in the '147 patent has multiple solvent switches and multiple concentration and purification steps. For instance, in Example 105, the procedure describes the use

of a water miscible organic solvent (DMF), followed by an organic mixture not miscible with water (hexane/MTBE) to extract the organic layers, followed by a water wash, followed by concentration, followed by dissolution in another organic solvent (xylenes), to yield the product.

Alternatively, the procedure described in the instant invention describes the use of organic solvents DMSO and toluene, followed by stirring and separation, followed by a water wash, followed by dissolution in methanol, to yield the product. The process described in the instant invention causes the intermediate to remain in the solution the entire time. In addition, because the organic layers do not have to be extracted, the purification is easier.

There is no teaching or motivation in the '147 patent to choose toluene and DMSO, nor is there a teaching to keep the intermediate in solution. Instead, the '147 patent requires multiple solvent switches and multiple concentration steps.

*The instant invention teaches a process that gives the product in a higher yield.*

The process of the instant invention gives the product in 85% yield, while utilizing significantly less solvent in a process with less purification steps. The processes described in Example 105 of the '147 patent result in 63% (beginning with the sulfonate salt) and 72% (beginning with the TsOH salt) yields, respectively. Applicants submit that an 18% difference in yield results in significant manufacturing savings.

Even if one of ordinary skill in the art had been motivated to alter the process disclosed in the '147 patent, there would have been no direction in the '147 patent regarding which specific reagents, solvents, amounts of solvents, temperature, additional steps and/or other conditions should have been employed in the process. From the discussion above, it is clear that one of ordinary skill in the art would not have simply had to choose from a finite number of identified, predictable solutions, with a reasonable expectation of success. Applicants respectfully submit that the '147 patent, taken as a whole, would not have provided teaching and/or direction and motivation for the particular conditions employed in each of the claimed reaction steps.

Accordingly, Applicants respectfully submit that the rejection of Claims 28 and 30-46 and under 35 U.S.C. § 103(a) as being obvious over Dorn et al. (U.S. Patent No. 5,719,147) be withdrawn.

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If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this response to Merck Deposit Account No. 13-2755.

Respectfully submitted,

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